Developmental Dental Aberrations After the Dioxin Accident in Seveso

Satu Alaluusua,[1,2] Pier Calderara,[1] Pier Mario Gerthoux,[3] Pirjo-Liisa Lukinmaa,[4] Outi Kovero,[5] Larry Needham,[6] Donald G. Patterson Jr.,[6] Jouko Tuomisto,[7] and Paolo Mocarelli[3]

[1]Department of Pedodontics and Orthodontics, Institute of Dentistry, University of Helsinki, Helsinki, Finland; [2]Department of Oral and Maxillofacial Diseases, Helsinki University Central Hospital, Helsinki, Finland; [3]Department of Laboratory Medicine, Desio Hospital, University of Milano, Bicocca, Italy; [4]Department of Oral Pathology, Institute of Dentistry, University of Helsinki, and Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland; [5]Department of Radiology, Institute of Dentistry, University of Helsinki, Helsinki, Finland; [6]Division of Laboratory Sciences, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [7]Department of Environmental Health, National Public Health Institute, and Department of Public Health and General Practice, University of Kuopio, Kuopio, Finland

Children's developing teeth may be sensitive to environmental dioxins, and in animal studies developing teeth are one of the most sensitive targets of toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Twenty-five years after the dioxin accident in Seveso, Italy, 48 subjects from the contaminated areas (zones A and B) and in patches lightly contaminated (zone R) were recruited for the examination of dental and oral aberrations. Subjects were randomly invited from those exposed in their childhood and for whom frozen serum samples were available. The subjects were frequency matched with 65 subjects from the surrounding non-ABR zone for age, sex, and education. Concentrations of TCDD in previously analyzed plasma samples (zone ABR subjects only) ranged from 23 to 26,000 ng/kg in serum lipid. Ninety-three percent (25 of 27) of the subjects who had developmental enamel defects had been < 5 years of age at the time of the accident. The prevalence of defects in this age group was 42% (15 of 36) in zone ABR subjects and 26% (10 of 39) in zone non-ABR subjects, correlating with serum TCDD levels ($p = 0.016$). Hypodontia was seen in 12.5% (6 of 48) and 4.6% (3 of 65) of the zone ABR and non-ABR subjects, respectively, also correlating with serum TCDD level ($p = 0.05$). In conclusion, developmental dental aberrations were associated with childhood exposure to TCDD. In contrast, dental caries and periodontal disease, both infectious in nature, and oral pigmentation and salivary flow rate were not related to the exposure. The results support our hypothesis that dioxins can interfere with human organogenesis. *Key words:* **developmental enamel defect, dioxin, hypodontia, hypomineralization, hypoplasia, Seveso, TCDD, teeth.** *Environ Health Perspect* **112:1313–1318 (2004). doi:10.1289/ehp.6920 available via *http://dx.doi.org/* [Online 1 July 2004]**

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is referred to as the most toxic man-made chemical known [International Agency for Research on Cancer (IARC) 1997]. Data on environmental accidents and occupationally exposed subjects have increased our knowledge on human health effects of TCDD (Sweeney and Mocarelli 2000).

The best-known dioxin accident took place in Seveso, Italy, in 1976. In a chemical factory, a trichlorophenol production reactor exploded and ≥ 30 kg TCDD was spread over an area of approximately 18 km^2 (Di Domenico et al. 1980). Several thousand people, children among them, were exposed to substantial quantities of TCDD. The contaminated area was divided into three major zones (A, B, and R) on the basis of decreasing order of surface soil concentrations of TCDD (Bisanti et al. 1980), and soon after the accident a health assessment of the population was initiated. As part of this effort, blood samples were collected for clinical chemistry tests, and small amounts of serum were stored for later analyses. These samples rendered it possible to quantify individual TCDD exposures (Mocarelli et al. 1988; Needham et al. 1997/1998).

Children exposed to TCDD had higher body burdens than adults. This was seen in zones A and B but also in the non-ABR zone surrounding the three major zones (Eskenazi et al. 2004). Approximately 20% of the children < 10 years of age who had been exposed and had been living in the most severely contaminated zone A developed chloracne (Mocarelli et al. 1986). Exposure of males before and during puberty was linked to a lower male:female ratio in their offspring, and it was suggested that TCDD permanently affected the function of human epididymis (Mocarelli et al. 2000).

In two episodes of epidemic poisoning in Japan and Taiwan (so-called Yusho and Yucheng accidents, respectively), severe developmental effects were observed in infants and children born to mothers who had been exposed to polychlorinated dibenzofurans/biphenyls (PCDFs/PCBs) (Rogan et al. 1988; Yamashita and Hayashi 1985; Yao et al. 2002). These included intrauterine growth retardation, low birth weight, hyperpigmentation, natal teeth, increased incidences of skin and respiratory infections, neurodevelopmental delay, and alterations in sexual development (Chen and Hsu 1994; Chen et al. 1992; Ikeda 1996; Rogan et al 1988).

Although there are differences among species in susceptibility, embryonic development of most vertebrate species is sensitive to TCDD (Peterson et al. 1993). Developmental effects in laboratory rodents include cleft palate, disturbed development of the mandible, various ureteric and kidney malformations in mice (Abbott and Birnbaum 1989; Abbott et al. 1987; Allen and Leam 2001; Peters et al. 1999), and alterations in the reproductive tract development and function in mice and rats (Hurst et al. 2000; Theobald and Peterson 1997). Impaired mammary gland development and differentiation were found in female mice after gestational and lactational exposure (Lewis et al. 2001). In rhesus macaques TCDD causes developmental jaw cysts (McNulty 1985), and in avian and fish embryos it causes cardiovascular toxicity and disturbs craniofacial development (Cantrell et al. 1996; Hornung et al. 1999; Teraoka et al. 2002; Walker and Catron 2000).

Teeth develop as a result of a series of inductive, sequential, and reciprocal interactions between the ectoderm and the subjacent mesenchyme (Thesleff et al. 1995). Tooth development is genetically regulated but sensitive to environmental disturbances. Aberrations in the function of tooth-forming cells lead to permanent morphologic consequences. Because development of the first primary tooth begins in the fourth week *in utero* and the development of the roots of the wisdom teeth is completed around 20 years of age, teeth serve as a record that covers a long time period of life.

We have shown that in a normal child population, polychlorinated dibenzo-*p*-dioxins (PCDDs) and PCDFs in mother's milk may cause mineralization defects in the child's permanent first molar teeth undergoing mineralization during the first 2 years of life

Address correspondence to S. Alaluusua, Department of Pedodontics and Orthodontics, Institute of Dentistry, P.O. Box 41, FIN-00014 University of Helsinki, Helsinki, Finland. Telephone: 358-9-19127314. Fax: 358-9-19127266. E-mail: satu.alaluusua@helsinki.fi

This work was supported by the European Commission (QLK4-1999-01446), Region Lombardia, Italy (2896), and the Research Program for Environmental Health, Academy of Finland (contract 203395). Planmeca Oy, Helsinki, Finland, provided us with a dental unit.

The authors declare they have no competing financial interests.

Received 17 December 2003; accepted 1 July 2004.